ISAKOS

International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine

12th Biennial ISAKOS Congress • May 12-16, 2019 • Cancun, Mexico

Paper #101

Beta-3 Adrenergic Receptor Agonist Improves Rotator Cuff Muscle Rehabilitation and Shoulder Function after Delayed Tendon Repair in Mice

Zili Wang, PhD, UNITED STATES
Xuhui Liu, MD, UNITED STATES
Mengyao Liu, BA, UNITED STATES
Carlin Lee, MD, UNITED STATES
Hubert Kim, MD, UNITED STATES
Brian Feeley, MD, UNITED STATES

Universtity of California San Francisco
San Francisco, CA, UNITED STATES

Summary:
Our results from this study showed that beta3 adrenergic receptor agonist can significantly improve muscle quality and shoulder function after delayed rotator cuff tendon repair

Abstract:

Purpose

The goal of this study is to test if Amibegron, a beta3 adrenergic receptor agonist, can induce fibro/adipogenic progenitors (FAPs) brown/beige adipose tissue (BAT) differentiation and improve rotator cuff (RC) muscle rehabilitation and shoulder function after delayed RC tear repair in a mouse model.

Methods

Five PDGFRa-GFP reporter mice, ten UCP1-knockout (KO) mice and ten of their colony control C57BL/6J mice at 3 months old underwent unilateral supraspinatus tendon transection surgery and 6 weeks delayed repair surgery (TT+DR). Another group of same number and strains mice at the same age underwent sham surgery to serve as control. 10mg/kg Amibegron or 5% DMSO vehicle was administered at the time of repair surgery through daily I.P. injection for 6 weeks. Gait analysis was conducted to measure shoulder function at 6 weeks after repair surgery, and animals were sacrificed at the same day. Supraspinatus muscle was harvested, and wet muscle weight was measured followed by frozen sectioning. UCP1, the hallmark protein expressed in BAT, was stained to assess the FAP BAT differentiation. Oil red O staining was used to assess fatty infiltration in muscle. Analysis of variance (ANOVA) with Tukey post hoc comparisons were used for statistical analysis.

Results

We found significant muscle atrophy, FI and upregulated UCP1 expression in the TT+DR group (muscle weight loss: -20.58% ± 3.04%, vs -1.97 ± 1.23% in sham, $p < 0.0001$; fat fraction area: 8.64% ± 3.41%, vs 0.77% ± 0.49% in sham, $p = 0.0009$; UCP1 fraction area: 2.74% ± 1.35%, vs 0.04% ± 0.03% in sham, $p = 0.0021$). In wild type mice,10mg/kg Amibegron significantly reduced muscle atrophy, FI and improved shoulder function in the TT+DR group (muscle weight loss: -10.31% ± 7.84%, vs -19.62 ± 3.33% in vehicle, $p = 0.0403$; fat fraction area: 5.37% ± 2.30%, vs 9.34% ± 1.51% in vehicle, $p = 0.0120$). However, Amibegron did not improve muscle atrophy, FI in the TT+DR group of UCP1 KO mice (muscle weight loss: -32.99% ± 6.66%, vs -33.39% ± 8.17% % in vehicle, $p = 0.9349$; fat fraction area: 12.68%

Paper #101

± 2.67%, vs 14.26% ± 2.29% in vehicle, p = 0.3461). Amibegron significantly improved shoulder function, as evidence as increased stride length and paw area in wildtype mice after RC repair. However, this effect was not seen in UCP1 KO mice.

Discussion

In this study, Amibegron, a beta3 adrenergic receptor agonist significantly reduced muscle atrophy and FI, and improved shoulder function after delayed RC repair. This result proved that reducing of muscle atrophy and FI can improve shoulder function after RC repair. As these effects were not seen with the UCP-1 KO mice, the effect of Amibegron appears to be due to a UCP1-dependent mechanism. We think amibegron-induced UCP-1 dependent FAP BAT differentiation may be the underline mechanism. Mirabegron, a beta3 adrenergic receptor agonist in the class of Amibergon that recently been approved by FDA to treat patients with hypersensitive bladders, could be used clinical to improve clinical outcome of RC repair patients in the future.